Substitute sheets for Figures 8 and 9 are attached. Both Figures now properly depict the fluorescence measured in Examples 2 and 3 and in the informal drawings as filed. Red-lined copies of the figures showing the changes made is attached herewith.

With respect to Figure 8, variant E146K is in fact the correct variant demonstrating agonistic activity similar to wild type TNF-a. The figure legend shows K112D as depicted as a darker plot than E146K, the graph properly reflects E146K as having the wild type like activity.

In addition substitute sheet for Figure 10A is provided. The changes were made to conform with the informal drawing as filed. Red-lined copies of the figure showing the change is attached herewith.

Claim Rejection under 35 USC §112, second paragraph

Claims 1 and 16 have been rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter the Applicants regard as their invention.

Claims 1 and 16 have also been rejected as being vague and indefinite for reciting the term "variant."

As stated in the MPEP §2173.05(a):

> The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. Applicants need not confine themselves to the terminology used in the prior art, but are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained. During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). See also MPEP § 2111 - § 2111.01. When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989).

In reviewing a claim for compliance with 35 U.S.C. §112, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required (See MPEP §2173.02). If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the

utilization and scope of the invention, and if the language is precise as the subject matter permits, the statute demands no more.

Applicants respectfully disagree because the Specification discloses the scope of what the term "variant" means in the present application. See Specification at page 2, lines 23-30; page 28, lines 4-13; and page 31, line 15-28.

The Examiner also states that the Applicants are claiming a product not by what it is, but rather what it is not.

> "The current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation. So long as the boundaries of the patent protection sought are set forth definitely, albeit negatively, the claim complies with the requirements of 35 U.S. 112, second paragraph." (MPEP 2173.05(i))

The Applicants point the Examiner's attention to the disclosure in the Specification where the variants are described as "non-naturally occurring." Specification at page 25, lines 20-33. As can be seen from the specification, "non-naturally occurring" is used to define the TNF variants of the present invention: ...by "non-naturally occurring" or "synthetic" or "recombinant" or grammatical equivalents thereof, herein is meant an amino acid sequence or a nucleotide sequence that is not found in nature; that is, an amino acid sequence or a nucleotide sequence that usually has been intentionally modified. See Specification at page 25, lines 20-33. Thus, this is not a limitation on the variants of the present invention, as they would not be found in nature. See Specification at page 22, lines 6-9. Furthermore, as discussed in the specification on page 22, at lines 6-9, the non-naturally occurring variants of the invention are most appropriately defined by their functional properties rather than their specific compositions. Variants that possess these properties can be readily produced and discovered by those skilled in the art. See Specification beginning at page 5, lines 30, ending on page 6, line 2.

In contrast, "naturally occurring" or "wild type" as used herein is a sequence found in nature and includes allelic variations, as opposed to sequences that have been intentionally modified. See Specification at page 25, lines 20-33. Therefore, the term "variant" is not vague and indefinite.

In response to the Examiner's inquiry about the receptor signaling, both receptors may be involved in TNF signaling. See Specification at page 23, lines 10-12.

In light of the above-arguments, the Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim Rejection under 35 USC §112, first paragraph

WRITTEN DESCRIPTION REJECTION:

Claims 1 and 16 have been rejected under 35 USC §112, first paragraph as containing subject matter which was not described in the specification in a way to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed.

The Examiner points out that the Specification meets the written description and enablement provisions of 35 USC §112, first paragraph for TNF-a substitutions at wild-type positions 21, 30, 31, 32, 33, 35, 65, 66, 67, 111, 112, 115, 140, 143, 144, 145, 146, and 147 (Figure 7).

However, the Examiner states that the Specification does not disclose all possible variants of TNF-a, which are not originally contemplated and fail to meet the written description provision, and thus fail to support the genus encompassed by the instant claims. The Revised Interim Guidelines for the Examination of Patent Applications Under the 35 USC 112, first paragraph "Written Description Requirement," Federal Register, Vol. 64, No. 244, pp 71427-71440, 71436 (Tuesday, December 21, 1999) state:

> "An applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention. [39] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[40] What is conventional or well known to one skilled in the art need not be disclosed in detail. [41]. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met."

...“For each claim drawn to a genus; for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction practice ..., reduction to drawings..., or by disclosure of relevant identifying characteristics, i.e., Structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.” “Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.”

...“A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption. The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In rejecting a claim, the examiner must set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should: 1) identify the claim limitation at issue; and 2) establish a prima facie case by providing reasons why a person skilled in the art at the time the invention was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed.”

Applicants submit that the invention as filed is complete by disclosure of sufficiently detailed relevant identifying characteristics, which provide evidence that Applicants were in possession of the claimed invention by disclosing other physical and/or chemical properties, functional characteristics and is coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Specification at beginning at page 5, lines 30, ending on page 6, line 2; page 11, lines 16-18; page 12, lines 4-16; page 17, lines 5-11; page 22, lines 6-9; page 25, lines 5-15; page 32, lines 4-40; Figure 7 and pages 53-60 (“Examples”).

Applicants assert support for the claimed genus is satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawing, and by disclosure of relevant identifying characteristics. See Specification at page 2, lines 25-26 and page 22, lines 6-9; beginning at page 24, line 27 and ending at page 26, line 4; Figure 4, Figure 7; and Examples 2 and 3. Finally, a person skilled in the art would recognize in the Applicants' disclosure a description of the invention defined by the claims, as evidenced by the enclosed factual declaration under 37 C.F.R. §1.132 and MPEP §716.09 from Robert Hayes, PhD stating that variant proteins designed utilizing a computational algorithm (e.g.

PDA™ technology) are functional for the biological property being tested. Therefore, a prima facie case to the contrary has not been demonstrated.

In *Vas-Cath Inc. v. Mahurkar* (19USPQ2d 1111, 1116), the court stated, "A fairly uniform standard for determining compliance with the "written description" requirement has been maintained throughout[.]" citing *In re Gosteli.* "Although [the applicant] does not have to describe exactly the subject matter claimed,... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed.Cir. 1989). The Vas-Cath court went on to state that: "The applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*" *Vas-Cath Inc. v. Mahurkar* (19USPQ2d 1111, 1117).

Applicants respectfully point the Examiner's attention to the application because there is disclosure on how to generate, analyze and test the variants of the claimed invention, as well as examples. See Specification at page 6, line 25-33, page 7, lines 12-17; page 8, lines 13-26; page 9, lines 21-36; page 11, lines 10-27; beginning on page 28, line 13, ending on page 29, line 4; page 40, lines 25-35; and pages 60-67. One skilled in the art would understand that the variants contemplated by the disclosure of specific positions would result in the modification of a desired property, while retaining both structure and function. A person skilled in the art would also appreciate the claimed variants without being required to envision all of the detailed chemicals structures of the polypeptides as asserted by the Examiner because the disclosed methods for generating the claimed variants are known in the art. See for example, Specification at page 2, lines 19-26; beginning at page 22, line 30, ending on page 24, line 15; page 31, lines 15-28; and page 32 lines 4-29.

With regard to the cited cases, *Fiers v. Revel*, 25 USPQ2d 16011, 1606(CAFC1993); *Amgen v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016; and *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, the Applicants respectfully point out that the cases may be distinguished from the instant case because each one spoke to the written description requirement regarding DNA or nucleic acid sequences. In contrast, the present invention is directed to amino acid sequences, which are not as variable as nucleic acids.

The Office Action states that only the isolated TNF-a polypeptide with substitutions at wild type positions 21, 30, 31, 32, 33, 35, 65, 66, 67, 111, 112, 115, 140, 143, 144, 145, 146, and 147 meets the written description requirement of §112, first paragraph. The Office Action also states that the "species specifically disclosed is not representative of the genus because the genus is highly variant." Applicants respectfully submit that the variant proteins of the present invention have at least one property critical for binding affinity altered as compared to the same property of wild type TNF-a. Specification at page 22, beginning at line 30, ending on page 23, line 1. The variant proteins may also have altered affinity toward oligomerization to wild type TNF-a. See Specification at page 23, lines 1-2 and lines 3-12. Therefore, although specific positions have been described, the protein properties sought are sufficiently described to demonstrate the Applicants were in possession of the polypeptide sequences set forth in Claims 1 and 16.

The Examiner has not made a prima facie showing that one skilled in the art would not have recognized the Applicants were in possession of the invention at the time the application was filed. In light of the foregoing, Applicants respectfully request the reconsideration and withdrawal of the written description requirement rejection.

ENABLEMENT:

Claims 1 and 16 have also been rejected because the specification, while enabling for TNF-a variants K112D, Y115T, D143K, D143R, Y115I, D143E, A145R, A145K, A145E, E146K and E146R does not reasonably provide enablement for all variant TNF-a. Further, the Examiner states that the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims.

The Applicants respectfully disagree for the following reasons. Section 112 does not require such extensive disclosure. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ81, 94 (Fed.Cir. 1986), cert.denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ481, 489 (Fed. Cir. 1984).

Furthermore, "[a]ll that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the scope of

enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." (See MPEP §2164.08)

The Examiner states that although it is known in the art that variants of a given polypeptide with amino acid deletions, insertions or substitutions the specification fails to provide any guidance regarding the changes/modifications contemplated and yet retain the function of the TNF-a variants claimed. Specification beginning at page 5, lines 30, ending on page 6, line 2.

The Applicants respectfully disagree because the Specification describes the variant proteins of the present invention. Applicants also submit that certain positions in a sequence are critical to the protein's structure function relationship. See Specification at page 11, lines 24-26. The variant proteins of the present invention have been designed with this critical relationship in mind. See Specification at page 11, lines 16-18 and page 31, lines 29-35. For example, the variant TNF-a protein is optimized by a well validated computational processing technology, i.e., PDA™ technology, resulting in a protein sequence that is generally different from the wild type TNF-a sequence in structural regions critical for receptor affinity, i.e. p55 or p75. Specification at page 19, lines 1-5. See for example, U.S. Patent Nos. 6,403,312; 6,188,965; 6,269,312; and PCT/US98/07254 and PCT/US01/40091. Thus, the present invention is directed to variant TNF-a proteins that are antagonists of wild type TNF-a. Specification at page 19, lines 6-9.

The variant TNF-a proteins of the present invention inhibits or significantly decrease the activation of receptor signaling by wild type TNF-a proteins. Furthermore, the variants of the present invention interact with the wild type TNF-a protein resulting in a complex incapable of activating TNF- receptors, i.e. p55 or p75. Specification at page 22, lines1-5. The variant TNF-a proteins also "form mixed-trimers with the wild type protein such that receptor binding does not occur and/or TNF-a signaling is not initiated." Specification at page 22, lines 6-10. The structural regions may be in direct contact with the receptor or distant but important for receptor binding via indirect contact through the protein structure. The mixed trimers of the present invention are monomers of wild type and variant proteins interact, forming trimeric TNF-a. Specification at page 22, lines 10-13.

The present invention also provides for variant TNF-a proteins that "exhibit decreased biological activity as compared to wild type TNF-a, including but not limited to, decreased

binding to the receptor, decreased activation and/or ultimately a loss of cytotoxic activity." Specification at page 22, lines 18-29. Additionally, altered protein properties of the variants of the present invention are described. Examples include, ability to bind to a receptor and ability to oligomerize, among others. See Specification at page 23, lines 18-27. As discussed below, modifications may be conservative or extreme to produce optimized sequences having the desired protein properties. Modifications contemplated by the present invention may also be evaluated de novo. See Specification at page 11, lines 31-32.

Additionally provided, are examples of small modifications are provided in the Specification at page 32, lines 4-9 and 10-29 and examples of more substantial changes in function and immunological identities are provided at page 32, lines 30-40. The Applicants respectfully points the Examiner's attention to the Specification at page 7, lines 12-33; page 8, lines 1-12; page 12, lines 4-23; page 13, lines 1-29; and page 31, lines 15-35.

Furthermore, the Examiner states the structural and functional requirements of the disclosed protein are lacking. The Applicants respectfully submit that the Examiner has overlooked the method(s) used to generate the variants, whereby the protein's structure and function are preserved. See Specification beginning at page 5, lines 30, ending on page 6, line 2; page 6, lines 3-8, and page 31, lines 26-28. See also U.S. Patent Nos. 6,403,312; 6,188,965; and 6,269,312.As discussed above, the variant proteins are not derived merely from sequence data as the Examiner suggests. See Specification at page 9 lines 21-36. Applicants submit the structural and functional requirements of TNF-a are well known in the art.

The Examiner states that it would require undue experimentation to practice the claimed invention. Whether or not undue experimentation is required to make and use an invention is to be determined based on several factors, including those enumerated in *In re Wands*, 858 F.2d 731, 73, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988):

1) The breadth of the claims;
2) The nature of the invention;
3) The state of the prior art;
4) The level of skill of the ordinary artisan;
5) The level of predictability in the art;
6) The amount of direction provided by the inventor;
7) The existence of working examples; an

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

As to the first factor, the breadth of the claims do not go beyond what is disclosed in the examples and is within the reach of the one of ordinary skill in the art, based on the disclosure and general knowledge in the art. See for example, Specification at page 22, lines 1-17 and page 31, lines 4-40.

With regard to the second factor, the nature of the invention, the nature of the invention is the generation of variant TNF-a protein sequences with specific functional properties. As shown above, this field is highly developed, based on both issued patents and publications, and thus lends itself to a finding of enablement. See for example Specification at page 19, lines 1-5 and U.S. Patent Nos. 6,403,312; 6,188,965; and 6,269,312; PCT/US98/07254 and PCT/US01/40091.

As to the third factor, the state of the prior art is very developed, with TNF-a being a well-known and well-characterized protein. See for example Specification beginning at page 1, line 9, ending on page 2, line 13 and U.S. Patent Nos. 6,403,312; 6,188,965; and 6,269,312; PCT/US98/07254 and PCT/US01/40091.

As to the fourth factor, the person of ordinary skill in the field of computational protein design or molecular biology is highly skilled.

As to the fifth factor, as discussed above, despite the assertions otherwise, the predictability in the field is reasonably high, particularly when *in vitro* results verified by well-known techniques are provided. See pages 53-60 ("Examples") and U.S. Pat. Nos. 6,188,965; 6,269,312; 6,403,312 and PCT/US98/07254 and PCT/US01/40091.

With respect to the sixth factor, the specification provides ample direction, and the knowledge in the field is very extensive regarding general techniques.

The seventh and eighth factors also dictate a finding of enablement, as the specification provides working examples. Figures 7, 8, 9, 10a and 10b. Furthermore, while some

experimentation would be necessary, it would not be considered other than routine, given the disclosure of the specification and the general knowledge in the field (*see* MPEP §2164.06).

As a preliminary matter, the present invention is drawn to compositions generated by a computational method for protein design. See for example, U.S. Pat. Nos. 6,188,965; 6,269,312; 6,403,312 and PCT/US98/07254 and PCT/US01/40091.

Applicants submit the test for enablement is whether one skilled in the art could make and use the invention from the disclosure without undue experimentation. In support of the enabling disclosure of the present application, examples that unequivocally show that variant proteins optimized for desired properties, generated by computational methods, are enabled and are listed in Dr. Hayes' declaration. See Hayes Declaration.

In the present Office Action, the Examiner states that the Applicants are only entitled to those variants having the disclosed amino acid residue modifications specified in the application. However, the invention described in the Specification is much broader than the variants disclosed. The variants contemplated by the invention are broader and the variants shown are certain embodiments within the scope of the invention. If the Applicants are only entitled to patent protection of specific variants actually disclosed in the present invention, others in the field would be able to easily, quickly and without undue experimentation make other variants of the present invention.

Applicants respectfully point to *In re Goffe*, 191 USPQ429 (CCPA 1976), where the court stated:

> "For all practical purposes, the Board would limit Appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found to work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts."

Additionally, in *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976), the court further stated:

> "Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is

> whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed."

Applicants believe the Examiner's proposed limitation of the present invention to only those variants actually disclosed in the Specification is unreasonable in light of *In re Goffe, In re Angstadt*, and the ease with which one skilled in the art could use the application as a guide to make and use variants of the invention with techniques known in the art to design around the variants of the invention.

The Examiner states that the application does not provide guidance as to the positions in the protein that are tolerant to change. See Specification at page 12, lines 4-16. The Applicants respectfully point to the disclosed positions specified in the application and figures. Also, see Specification at page 2, lines 25-26 and Figure 7. Additionally, the Examiner states that regions affecting binding, activity, three-dimensional spatial orientation of binding and active sites and determinants of antigenicity can tolerate only relatively conservative substitutions or no substitutions and that the Applicants have not disclosed the nature and extent of changes that may be made at the specified positions. Applicants disagree because the specification, in fact, discloses the nature and extent of the modifications made. See Specification at page 12, lines 4-16; page 17, lines 5-11; page 25, lines 5-15 and page 32, lines 4-40. Positions critical to receptor binding were selected for modification in order to disrupt receptor binding but not disrupt association with TNF monomers or the protein structure. It is well known to those in the art that such positions are indeed more tolerant to change.

The Applicants submit the Examiner has mischaracterized the Wells and Ngo publications because neither says that any particular region is limited in the substitutions, which may be made, but rather that some mutations may cause additivity in mutational effects (Wells) and that some computational algorithms present challenges in de novo protein structure prediction without prior information determining a protein's three-dimensional structure (Ngo). Neither publication states nor suggests that computationally designed protein variants cannot be

functional proteins. The variant proteins of the present invention are generated with an atomic-level three-dimensional structure of TNF-a, using a well-tuned algorithm (e.g. PDA™ technology) to allow modification without adversely affecting the structure and function or disrupting the local structure of the protein. Applicants respectfully submit that the art of protein design has progressed significantly from the dates of publication of the cited references. See for example, U.S. Patent Nos. 6,403,312; 6,188,965; 6,269,312; and PCT/US98/07254 and PCT/US01/40091. Those skilled in the art regularly create variant proteins that retain structure and function, using a wide variety of methods. A discussion of the advances in protein design may be found in the publication, "Proteins from Scratch" by William F. DeGrado. (DeGrado, William F., "Proteins from Scratch," Science, 3 October 1997, Volume 278, pp. 80-81.) A copy of this publication has been enclosed herewith for the Examiner's convenience.

In conclusion, Applicants submit that the Specification taken in conjunction with the state of the art at the time the invention was filed fully enables a person skilled in the art to practice the method of the invention without undue experimentation. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim Rejection under 35 USC §102

Claims 1, 2, 14, 15, and 16 have been rejected under 35 USC §102(b) as being anticipated by Banner et al. (U.S. Pat No. 5, 597,899). The Examiner asserts that the mutations made by Banner have the inherent feature of forming mixed trimers, thus anticipating Claims 1, 2, 14, 15, and 16. Applicants disagree for the following reasons.

Banner teaches the production of mutations at several different amino acid positions compared to wild type TNF-a, which has different binding affinity to p55-TNFR compared to p75 TNFR. Banner also teaches multiple amino acid substitutions compared to wild type TNF-a and the recovery of variant TNF-a proteins. However, as the Examiner notes, Banner does not teach the formation of mixed trimer formation due to the presence of variant TNF-a.

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail

as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)."

The Examiner has mischaracterized Banner, which does not suggest, teach or disclose exchange between the mutants and wild type TNF-a to form mixed trimers. Rather, Banner teaches the discovery of non-mixed trimeric variants that have changes in their relative receptor signaling properties, with the goal of discovering TNF-a variants useful for the treatment of cancer.

In contrast, the present invention teaches the formation of mixed trimers that are incapable of activating receptor signaling. The present invention is directed to modified TNF-a monomers, which exchange or interacts (e.g., trimerize) with wild type TNF-a, thus sequestering wild type TNF-a into a complex incapable of signaling. See Specification at page 2, lines 19-26 and page 23, lines 3-12.

As can be seen from the above discussion, Banner et al. does not suggest, teach or disclose exchange between the mutants and wild-type TNF alpha to form mixed trimers. Therefore, Banner et al. does not teach each and every element of the invention as claimed, the cited reference does not anticipate the invention. Therefore, the Applicants request withdrawal of the rejection.

Claim Rejection under 35 USC §103

Claims 3 and 13 have been rejected under 35 USC §103 as being unpatentable over Banner et al.

Applicants confirm that the subject matter of the cited claims were commonly owned at the time the invention was filed.

To establish a *prima facie* case of obviousness, three basic criteria must be met: 1) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach or suggest all the claim limitations. (See MPEP 2142).

"A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert denied, 469 U.S. 851 (1984)."

The statements made about Banner et al. above are equally applicable here. There is no suggestion or motivation to modify Banner to form mixed trimers incapable of activating receptor signaling because Banner teaches modifying binding affinity, to increase the binding affinity for the p75 receptor over the p55 receptor. There is no discussion of a reasonable expectation of success in Banner as to the variants of the present invention. Finally, the Examiner has conceded that Banner does not teach the formation of mixed trimer formation due to the presence of variant TNF-a. Furthermore, Banner does not teach or suggest forming mixed trimers incapable of activating receptor signaling. Banner, when considered as a whole, leads away from the claimed invention because Banner seeks to increase binding affinity for p75.

In contrast, the present invention sequesters wild type TNF-a to prevent any receptor binding and/or preventing TNF-a signaling. See Specification at page 22, lines 6-9 and page 23, lines 3-12.

In conclusion, for the above-stated reasons Banner does not obviate the present invention. In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under §103.

The Applicants submit that in light of the above-amendment and argument, the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the Specification by the "Amendment". The attached page is captioned **"Version with markings to show changes made."** An **"Appendix of Pending Claims"** has been attached for the Examiner's convenience.

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Dated: 2/4/03

Respectfully submitted,
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VERSION TO SHOW CHANGES MADE

Page 7, lines 1–8.

The source of the sequences can vary widely, and include taking sequences from one or more of the known databases, including, but not limited to, SCOP (Hubbard, et al., Nucleic Acids Res 27(1):254-256. (1999)); PFAM (Bateman, et al., Nucleic Acids Res 27(1):260-262. (1999)); VAST (Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996)); CATH (Orengo, et al., Structure 5(8):1093-1108. (1997)); PhD Predictor [(http://www.embl-heidelberg.de/predictprotein /predictprotein.html)] **Predictor (Rost, B. Sander, C., and Schneider, R.,PHD--an automatic mail server for protein secondary structure prediction. Comput Appl Biosci. 1994 Feb;10(1):53-60)**; Prosite (Hofmann, et al., Nucleic Acids Res 27(1):215-219. (1999)); PIR [(http://www.mips.biochem.mpg.de/proj/protseqdb/)]; GenBank [(http://www.ncbi.nlm.nih.gov/)] **(Wu CH, Yeh LS, Huang H, Arminski L, Castro-Alvear J, Chen Y, Hu Z, Kourtesis P, Ledley RS, Suzek BE, Vinayaka CR, Zhang J, Barker WC, The Protein Information Resource. Nucleic Acids Res. 2003 Jan 1;31(1):345-7);** PDB [(www.rcsb.org)] **H. M. Berman, T. Battistuz, T. N. Bhat, W. F. Bluhm, P. E. Bourne, K. Burkhardt, Z. Feng, G. L. Gilliland, L. Iype, S. Jain, P. Fagan, J. Marvin, D. Padilla, V. Ravichandran, B. Schneider, N. Thanki, H. Weissig, J. D. Westbrook and C. Zardecki, Acta Cryst., The Protein Data Bank (2002). D58, 899-907**; and BIND (Bader, et al., Nucleic Acids Res 29(1):242-245. (2001)).

Page 8, lines 1-12.

Similarly, structural alignment of structurally related proteins can be done to generate sequence alignments. There are a wide variety of such structural alignment programs known. See for example VAST from the NCBI [(http://www.ncbi.nlm.nih.gov:80/Structure/VAST/vast.shtml)] **(Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996)**; SSAP (Orengo and Taylor, Methods Enzymol 266(617-635 (1996)) SARF2 (Alexandrov, Protein Eng 9(9):727-732. (1996)) CE (Shindyalov and Bourne, Protein Eng 11(9):739-747. (1998)); (Orengo et al., Structure 5(8):1093-108 (1997); Dali (Holm et al., Nucleic Acid Res. 26(1):316-9 (1998), all of which are incorporated by reference). These sequence alignments can then be examined to determine the observed

sequence variations. Libraries can be generated by predicting secondary structure from sequence, and then selecting sequences that are compatible with the predicted secondary structure. There are a number of secondary structure prediction methods such as helix-coil transition theory (Munoz and Serrano, Biopolymers 41:495, 1997), neural networks, local structure alignment and others (e.g., see in Selbig et al., Bioinformatics 15:1039-46, 1999).

Page 12, lines 12-16

Similarly, residues which may be chosen as variable residues may be those that confer undesirable biological attributes, such as susceptibility to proteolytic degradation, dimerization or aggregation sites, glycosylation sites which may lead to immune responses, unwanted binding activity, unwanted allostery, undesirable enzyme activity but with a preservation of binding, etc. In the present invention, it is the [tetramerization] oligomerization domain residues which are varied, as outlined below.

APPENDIX OF PENDING CLAIMS

1. (Amended) A non-naturally occurring variant TNF-α protein comprising an amino acid sequence that has at least one amino acid substitution as compared to the wild-type TNF-α sequence, wherein said variant TNF-α protein will interact with the wild-type TNF-α to form mixed trimers incapable of activating receptor signaling.

2. A non-naturally occurring TNF-α protein according to claim 1 wherein said TNF-α protein has from 3 to 5 amino acid substitutions as compared to wild-type TNF-α sequence.

3. The non-naturally occurring TNF-α protein according to claim 1, wherein said substitutions are selected from the group of substitutions consisting of K112D, Y115T, D143K, D143R, and Y115I.

13. The non-naturally occurring TNF-α protein according to claim 3, wherein said substitution consists of Y115T (SEQ ID NO:20).

14. The non-naturally occurring TNF-α protein according to claim 1, wherein said substitutions are selected from amino acid residues at positions 21, 30, 31, 32, 33, 35, 65, 66, 67, 111, 112, 115, 140, 143, 144, 145, 146 and 147.

15. The non-naturally occurring TNF-α protein according to claim 14, wherein said substitutions are selected from the group of substitutions consisting of D143E, D143N, D143S, A145R, A145K, A145E, E146K, E146R and A84V.

16. A method of recovering a non-naturally occurring variant TNF-α protein comprising an amino acid sequence that has at least one amino acid substitution as compared to the wild-type TNF-α sequence, wherein said variant TNF-α protein will preferentially interact with the wild-type TNF-α to form mixed trimers incapable of activating receptor signaling, from a host cell.

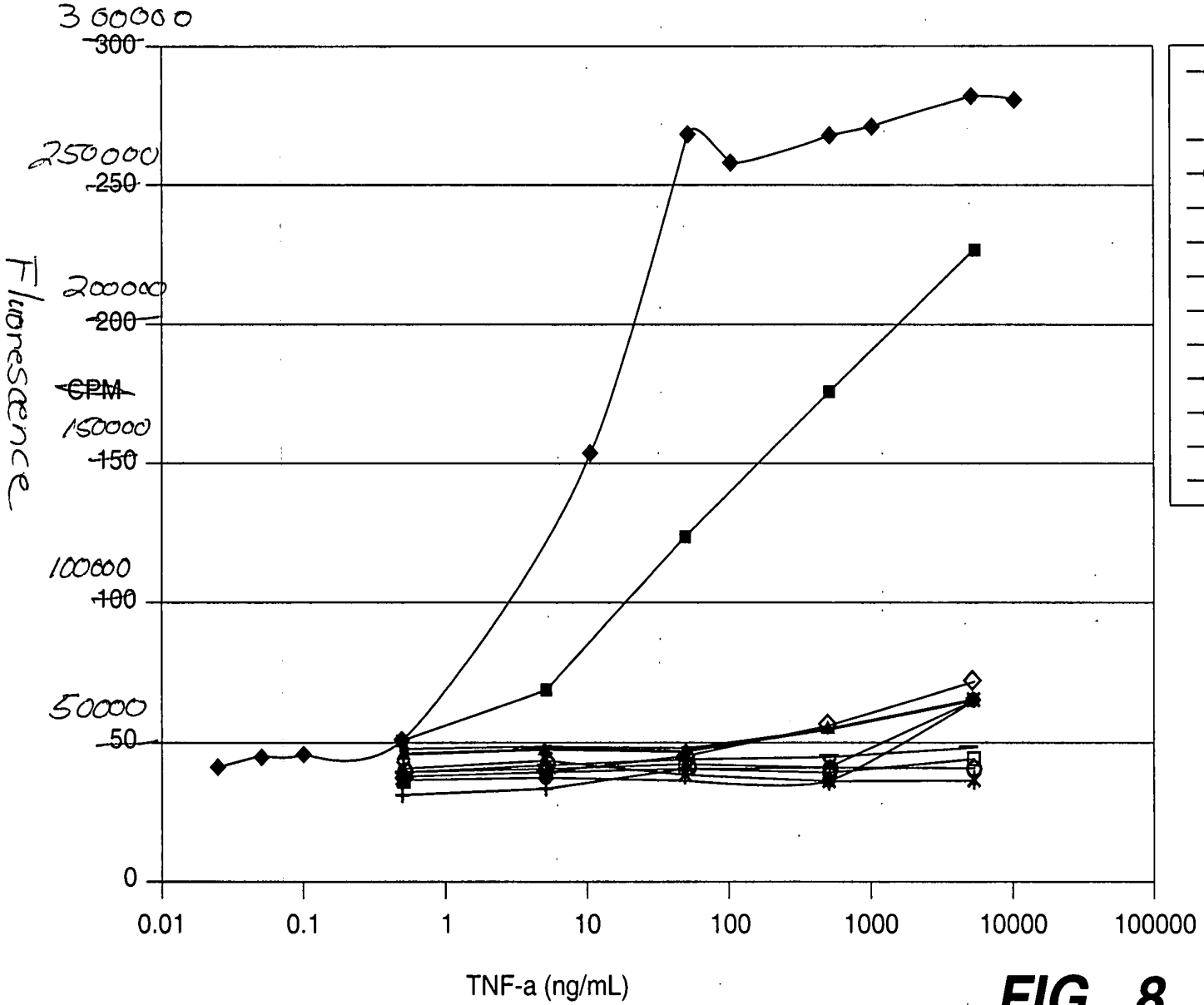

FIG._8

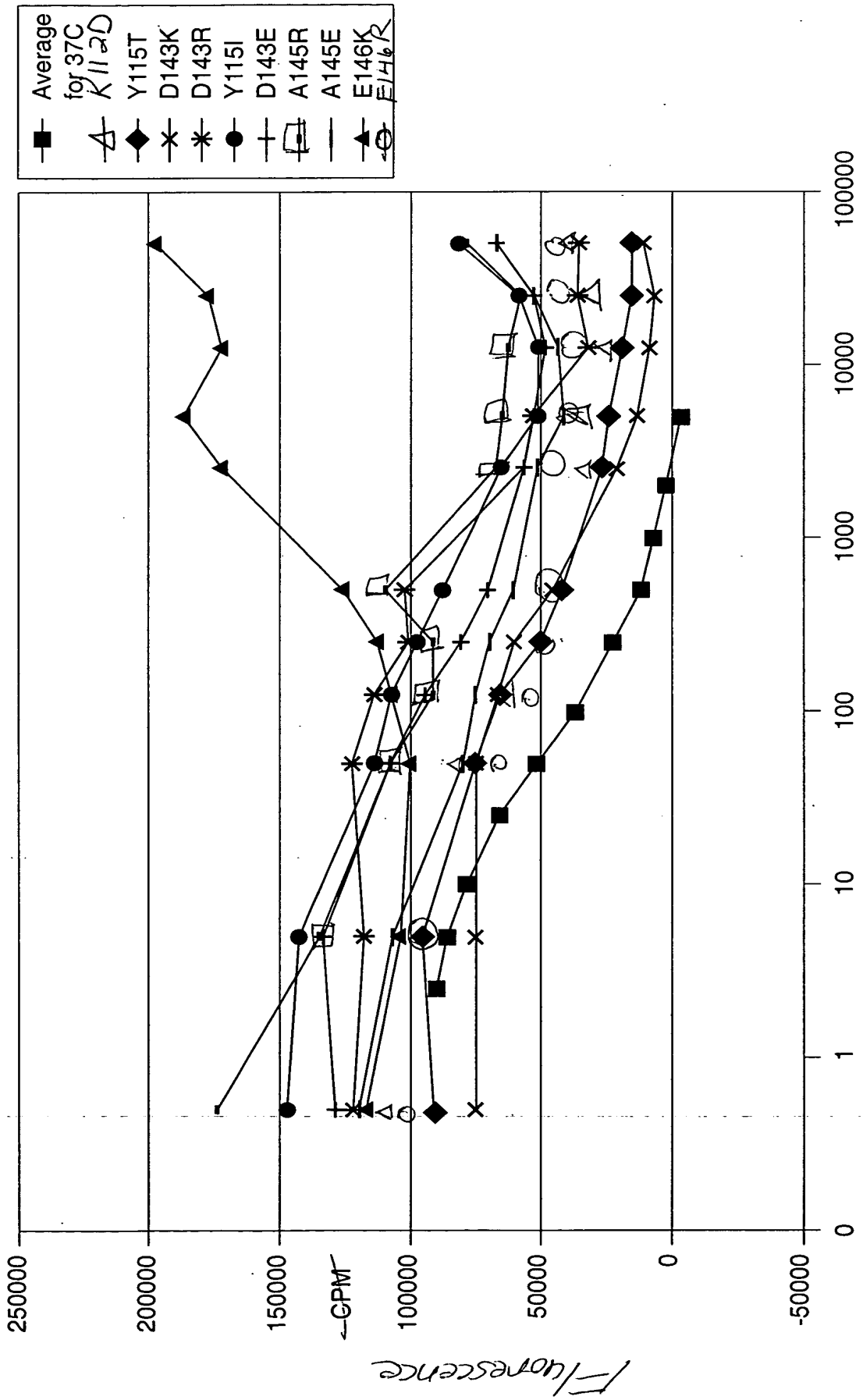

FIG._9

D143R

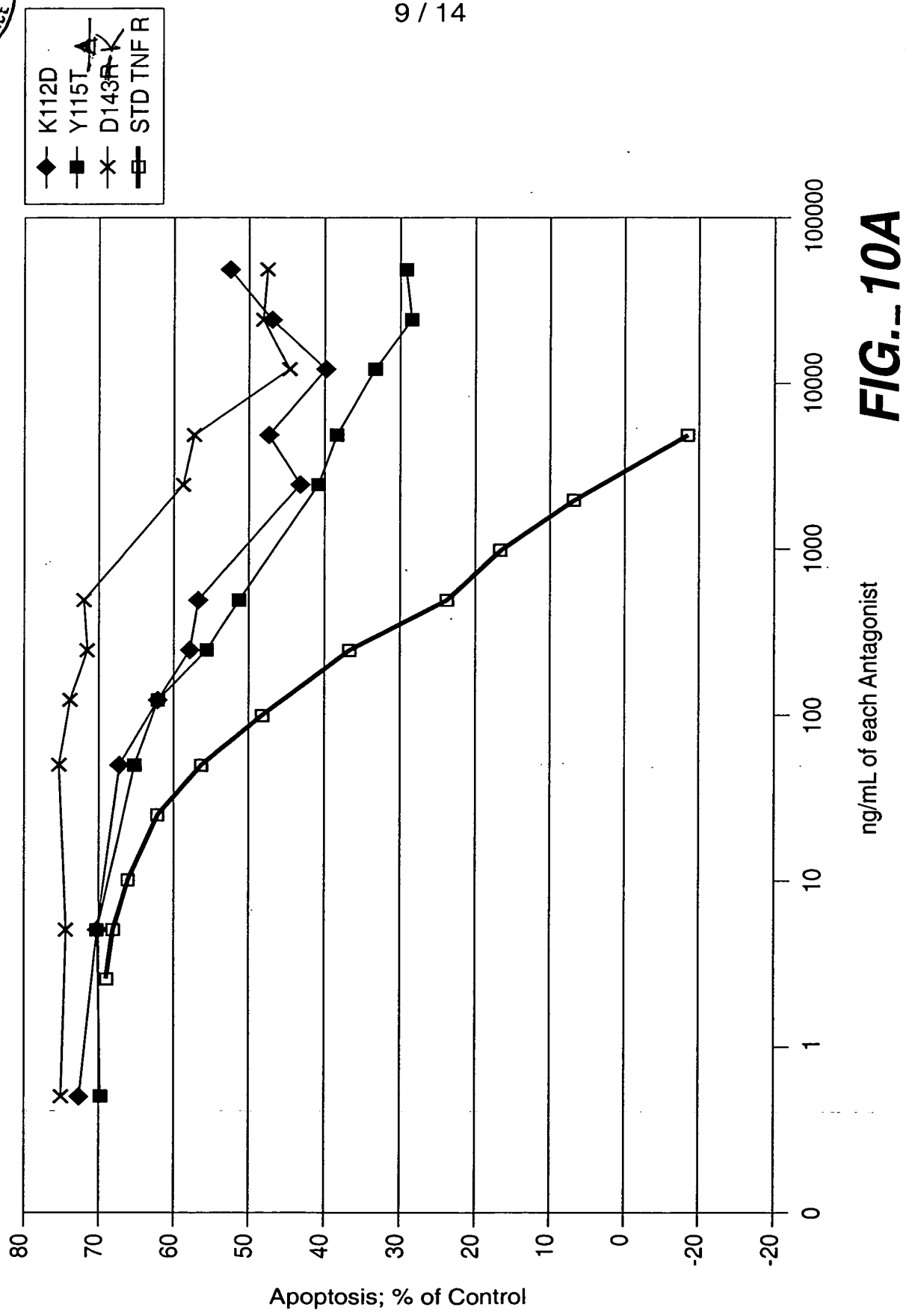

FIG._10A